Heart Transplantation

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Although the number of available donor hearts severely limits the epidemiologic impact of heart transplantation on patients with heart failure, patients with end-stage heart failure unresponsive to medical management currently have no other viable alternatives. Destination therapy with a ventricular assist device is the closest toward approaching clinical reality but has been plagued with problems of infection and stroke. The purpose of this review is to summarize recent developments in the field that may broaden the clinical impact of heart transplantation. For example, novel methods of cardiac preservation are being designed to safely evaluate and utilize "extended criteria" donors. Surgical techniques and medical management have reduced the incidence of postoperative right heart failure, and immunosuppressive regimens promise to limit chronic graft vascular disease.

Key words: *heart transplantation, review, surgical technique, immunosuppression*

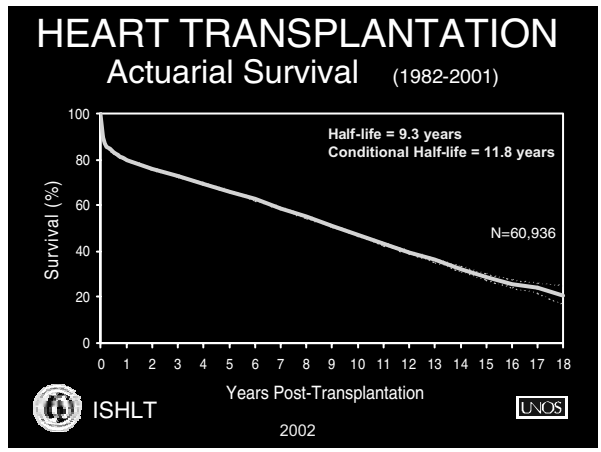

Fig 1. Actuarial survival following heart transplantation.

The incidence of end stage heart failure is growing along with the population of the United States. Several novel therapies have been heavily investigated to address this problem: chronic mechanical assistance of the ventricle, myocyte transplantation to revive the failing heart, and xenotransplantation of a pig or primate heart. However, it is unlikely that any of these promising therapies will soon approach the impact on quality of life and survival that allogenic heart transplantation has made over the past 35 years (Figure 1). The purpose of this review is to highlight some of the challenges that persist in this field.

Recipient Listing

The process of cardiac transplantation begins with the acceptance of a donor organ that has been offered through the United Network of Organ Sharing (UNOS) matching system. A blood type–compatible donor heart is matched to a recipient based on characteristics such as height, weight, medical status, and time accrued on the waiting list. The thoracic organ waiting list is stratified by 3 levels: status 1a, 1b, and 2 (UNOS Policy 3.7.3). Status 1a is defined by the need for ICU care with high-dose inotropes or mechanical assistance including intra-aortic balloon pump. Although this status was initially granted for the first 30 days of mechanical assist, recent revision in policy has resulted in the selection of a 30-day window for listing as 1a at any point after implantation. This arose from the experience of early post-pump implants as a higher risk for transplant. Because infection and stroke are common with these devices, it is reasonable to afford these bridge patients a short period when they are prioritized prior to a complication but after recovery from the implant. After the 30-day window period, a complication due to a ventricular assist device (e.g., infection) is another, more controversial, method of being relisted as status 1a [1]. Heart transplant candidates who have a chronic mechanical assist device or who are inotrope dependent are granted status 1b. All other patients with compensated heart failure managed as outpatients are status 2.

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The mortality of patients while on the waiting list is currently estimated at 10% per year [2]. This mortality can be minimized by a clear understanding of the "transplantation window," meaning the patient is sick enough to require transplantation but does not have decompensated cardiogenic shock and irreversible multiorgan failure. While the ejection fraction is a useful screening test for heart failure, the peak oxygen consumption on exercise testing (peak VO_2) is widely regarded as the best way to quantify this "window." Specifically, a peak VO_2 < 14 ml/min/kg is predictive of failure of medical management and the need for transplantation [3].

According to UNOS, there are 3894 heart transplant candidates as of January 31, 2003, which far exceeds the approximately 2200 transplants performed in the United States each year [4]. Therefore, all reasonable nontransplant options should be exhausted in candidates for transplantation. Optimal medical therapy includes agents such as ACEI and beta-blockers at the maximal tolerable doses. Further inhibition of the renin-angiotensin-aldosterone system by aldactone has been shown to improve mortality and therefore potentially avoid transplantation [5]. Biventricular pacing may be indicated in 50% of heart failure patients with interventricular conduction delay > 130 msec. This rather innocuous therapy has been shown to improve symptoms and decrease the need for hospitalization in the MIRACLE trial [6]. Automatic defibrillators have been recently shown to reduce mortality in ischemic cardiomyopathy in the MADIT I and II trials. Paradoxically, defibrillators may enhance the development of heart failure [7] simply as a byproduct of the effective prevention of sudden death or from an undefined effect of the defibrillator such as asynchronous pacing. Increasingly, coronary bypass grafting is being offered to cardiomyopathy patients with good coronary targets and reversible ischemia on viability studies [8]. The surprising and immediate improvement in ventricular function following mitral valve repair in those with a dilated annulus due to progressive ischemic and nonischemic cardiomyopathy is thought secondary to an acute reduction in wall tension from reduced ventricular preload (i.e., the Law of Laplace's takes precedence over the Frank-Starling Law) [9]. Finally, "bridge to transplant" by a ventricular assist device (VAD) has proven to improve end-organ resuscitation and enhance physical therapy. Furthermore, the need for inotropes that may enhance heart failure and arrhythmias is eliminated. Although a VAD increases the technical challenge of heart transplantation, the posttransplant mortality is now similar to status 2 patients. Compared to similar patients on preoperative high-dose inotropes, the morbidity of heart transplantation for patients on a VAD is improved with significant reductions in perioperative renal (52.6% versus 16.7%) and right heart (31.6% versus 5.6%) failure [10]. Unfortunately, the onset of a blood-stream infection eliminates the benefit of a VAD [1]. Sepsis was the most common cause of mortality during the randomized destination VAD versus medical therapy (REMATCH) trial [11]. Rational efforts to minimize infection include tight perioperative glucose control [12] and nutritional support [13], elimination of nasal *Staphylococcus aureus* [14], and protocols for driveline care. Recently, data have suggested that the biomaterial-blood interface also reduces cell-mediated and antibody-dependent immunity [15].

Donor Selection

Due to inadequate supply of donor organs, heart transplantation has fallen well short of being a viable epidemiologic solution for end-stage heart disease. Recently, kidney transplantation has enjoyed a growth in the number of donations largely due to "extended criteria" and non-heart-beating donors. Application of these innovative measures in heart transplantation has been limited due to concerns of exacerbating the most common cause of 30-day mortality: primary graft nonfunction [16]. While a kidney transplant recipient with this complication may return back to dialysis, primary nonfunction invariably leads to mortality in heart transplant patients.

Hemodynamic collapse and cardiac arrest are the natural history of brain death [17]. Therefore, aggressive optimization of the donor must immediately follow the diagnosis of brain death. During their prior management by the neurosurgical team, donors are often given large doses of vasopressors with subsequent volume depletion for the purposes of optimizing brain perfusion. Pulmonary artery catheterization and echocardiography can provide guidance on appropriate fluid management. In addition, large doses of inotropes are often the result of hormonal deficiencies that develop after brain death. Donor infusions of glucose/insulin/potassium, triiodothryonine (T3), and cortisol have been shown to reduce donor inotropic requirements and improve recipient outcome following transplantation [18] and are recommended in a recent consensus statement [19].

The pathophysiological changes in the donor heart initiated by brain death are enhanced by subsequent events such as graft harvest, storage, and reperfusion. Graft ischemic time, while relatively less potent as an isolated risk factor, interacts with other risk factors present in the "extended criteria donor" to synergistically increase recipient mortality [16]. Therefore, expanding the cardiac donor pool may await the development of a clinically relevant graft preservation system that minimizes the effect of ischemia. The use of a continuous perfusion system during the ex vivo preservation period has been shown to neutralize the effect of the ischemic transport time on graft outcome, clinically in renal transplants [20] and experimentally in large animal heart transplant models [21]. Recirculation of oxygenated blood or asanguinous preservation solutions at warm or cold temperatures have been used for the purposes of preventing the anaerobic metabolism that occurs during the standard cold storage method.

Despite its increased complexity, this method of preservation provides many potential advantages for clinical heart transplantation. It would allow pretransplant, ex vivo evaluation of these extended criteria donor organs to minimize the recipient's risk of developing primary graft nonfunction while maximizing use of the donor pool. Continuous perfusion has been shown to preserve the graft endothelium better than static cold storage and may provide time for a reversal of the activated coronary phenotype. A growing body of evidence points to the activation of the endothelium as a major factor in the development of reperfusion injury, primary graft dysfunction, and acute and chronic rejection [22,23]. Extension of the acceptable ex vivo preservation period using continuous perfusion would potentially allow for the implementation of an HLA matching system similar to kidney transplantation. Two large databases, the UNOS/ISHLT [24] and CTSG [25] Registries, have revealed a long-term benefit to HLA matching similar to that seen in renal transplantation.

Heart Transplantation

The issues surrounding the performance of heart transplantation remain similar to that originally outlined by Shumway, with a few notable exceptions. The morbidity of what are frequently redo operations with long cardiopulmonary bypass times has been reduced by the hemostatic agent aprotinin [26]. By inhibiting serine proteases, aprotinin has been shown to block plasminogen activators and therefore fibrinolysis while also inhibiting thrombin and therefore the CPB mediated "exhaustion" of platelets. The limitation of blood product usage has been shown to have a wide range of benefits in heart surgery, which are amplified in the transplant patient. Complementary to aprotinin is the use of a Thrombelastography™ (Haemoscope, Niles, IL) based transfusion algorithm, which more accurately predicts the risk for bleeding than conventional measures of the hemostatic system such as platelet count, PT/PTT, and fibrinogen [27]. This algorithm limits the number of empirically given, unnecessary transfusions, which likely increase the risk of hypercoagulability and, potentially, thrombotic events [28].

The most notable technical modification has been the substitution of the bicaval anastomoses for the earlier atrial-to-atrial cuff technique. The original heart transplantation involved 4 anastomoses: the aorta, pulmonary artery, and the 2 atrial cuffs. For the atrial cuffs, the donor's atria are opened and sewn to a cuff of the respective atria of the recipient (Figure 2). While simple, several problems have been noted in the allograft that are thought to be related to this bi-atrial cuff technique: dissyncrony between donor and recipient atria leading to AV valve regurgitation and reduced RV filling, increased trauma to the sinus node leading to a lowered rate of postoperative normal sinus rhythm, and technical difficulties with obtaining endomyocardial biopsies via right heart catheterization. These findings led to the modification in which anastomoses were performed between the superior and inferior cavae of the donor and recipient leaving the right atrium intact. Using the bicaval technique, several retrospective analyses have shown an improvement in allograft performance. A randomized trial comparing the bicaval versus the standard atrial cuff methods found an improvement in mortality using the bicaval technique [29].

Perioperative Management

The improved mortality following the bicaval technique is in large part due to improved right heart function. Difficulties with the right heart are the most common cause of primary graft dysfunction noted following weaning from cardiopulmonary bypass. Reasons for the problems noted with the right heart are not entirely clear but related to the acute changes in pulmonary vascular resistance that the heart is required to work against in the pre-

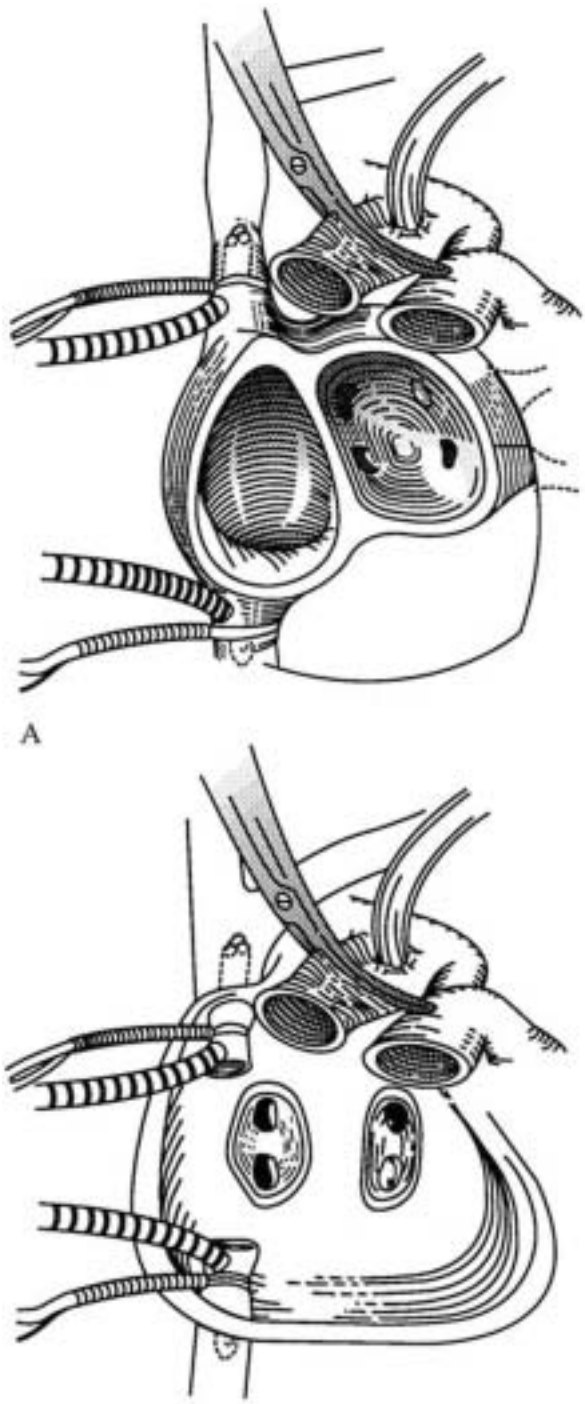

Fig. 2. Donor cardiectomy for biatrial cuff (A) and bicaval (B) anastomoses. Reprinted with permission from both Society of Thoracic Surgeons (*Ann Thorac Surg*. 1999;68:1242-1246) and Nizar A. Yonan, FRCS.

viously healthy donor versus the recipient with end-stage heart failure. In addition, the most common wall motion abnormality seen in donor hearts before and after transplantation is septal hypokinesis. In the donor, this pattern of hypokinesia is thought due to the enhanced sympathetic innervation of the septum over other areas and therefore greater potential for injury following the "autonomic storm" that follows brain death [30]. This initial damage predisposes the septum to the cumulative injuries that follow: graft harvest, ischemia, reperfusion, and reimplantation in an "activated" host. Right heart failure results in part due to the relatively greater role the septum plays in right versus left heart systolic function [31]. Additionally, diastolic dysfunction is induced by ischemia-reperfusion injury in both chambers but is less tolerated on the right side because of its predominant role as a compliance chamber [32]. Treatment of posttransplant right heart failure involves avoiding factors that increase right heart afterload (e.g., hypoxia, acidosis, excessive blood product transfusions) and using agents to reduce it (e.g., dobutamine, milrinone, inhaled nitric oxide). In addition, the intraaortic balloon pump has also been shown to be of benefit in posttransplant right heart failure. Although it is often thought of only as a means of addressing left heart failure, the balloon pump augments coronary blood flow and therefore improves the function of the septum and right ventricular free wall [33]. Given their potential beneficial effect against donor heart reperfusion injury, aprotinin, leukocyte filters, and NO are strongly considered in recipients receiving a heart at increased risk for right-sided failure.

An elevated CVP in the setting of low cardiac output and reduced LV filling and septal dyskinesis by echocardiography establishes the diagnosis in most severe cases of RV dysfunction. However, part of the difficulty in managing right heart failure is making an accurate diagnosis and monitoring response to treatment of milder degrees of RV dysfunction. Echocardiography, which has been a major advance for monitoring left heart function, typically obtains images of the crescent-shaped right heart that are an insensitive measure of function. RV ejection fraction is a particularly poor predictor of true right ventricular function given its relatively greater dependence on loading conditions (i.e., pre/afterload). Tissue Doppler imaging has the potential to assess contractile function independent of ventricular shape. This method has been validated in a recent animal study against the "gold standard" of invasive pressure/volume relationships to measure the end systolic pressure/volume curve [34]. The use of commercially available conductance catheters, which measure RVEF and RVEDV, allows the derivation of this curve, providing a clinically relevant assessment of RV

function [35], but awaits further analysis in transplant patients.

An unusual cause of primary graft failure is hyperacute rejection (HAR), indicated by the gross anatomical findings of edema, hemorrhage, and thrombosis shortly following revascularization. This process involves preformed antibodies that immediately bind to and activate the endothelium, initiating the complement and coagulation cascades. These antibodies bind to oligosaccharide antigens of the ABO blood group that are similar to those found on numerous endemic bacteria, protozoa, and viruses. The cross-reactivity of antibodies directed against these endemic microbes is likely to be responsible for the preexisting natural antibodies that cause HAR after ABO-incompatible organs. Because the titer and avidity of preformed antibodies against the blood group antigens in newborn infants is low, ABO-incompatible cardiac allografts have shown greater success in these patients [36]. HAR also occurs from antibodies directed against donor human leukocyte antigen (HLA) Class I major histocompatibility complex (MHC) antigens that are constrictively expressed by allograft endothelium. The likelihood of anti-MHC Class I antibodies is increased in patients with a prior history of exposure to allogenic HLA through prior blood transfusions, pregnancy, or recent mechanical support associated with blood product transfusions, especially platelets that express abundant MHC Class I antigen. If the transfusion of blood or platelets is required in a transplant candidate, the use of leukocyte-depleted transfusions can reduce the risk of HLA exposure [37]. CMV infection is known to increase the expression of HLA on platelets and contaminating leukocytes, and therefore CMV-negative blood should be used regardless of the CMV status of the recipient [37].

Candidates with preexisting HLA Class I antibodies have benefited by strategies designed to reduce circulating antibodies and B-cell antibody production [38]. Perioperative regimens of plasmapheresis and/or intravenous immunoglobulin (IVIG) and cytoxan continued posttransplantation have reduced HLA Class I antibodies and improved upon the likelihood of finding a negative donor. This use of aggressive posttransplant regimen has avoided HAR after transplantation despite a positive prospective cross-match [39]. IVIG may have its effect by anti-idiotypic antibodies; antibodies against membrane molecules, including CD4 and CD8; or soluble forms of HLA molecules. Recently, monthly cyclophosphamide (0.5-1.0 gm/M^2) was shown to be effective against B-cell antibody production [40]. Antidonor HLA antibodies have developed in some after transplant despite a negative prospective cross-match. Titers may rise as early as 3-4 days after transplant, which implies a secondary antibody response with undetectable levels of preformed anti-HLA antibodies despite prior exposure. Although a process known as accelerated, acellular rejection occurs in a few, the induction of a protective phenotype (e.g., bcl-x_L, bcl-2, and A20) inhibits endothelial activation and prevents vascular injury in the vast majority [41]. As T lymphocytes express MHC Class I antigens, the presence of preformed lymphocytotoxic antibodies, especially IgG isotype, detected on routine T-cell cross-match to donor blood is considered a contraindication to transplantation. Transplant candidates are routinely screened for these antibodies during the evaluation period. Candidate serum is tested against a panel of volunteers who contain the major HLA allotypes. The percentage of panels that demonstrate a reaction is referred to as measurement of panel-reactive antibodies (PRA). Patients with a high degree of "sensitization" to the donor panel (PRA > 10%-20%) are at risk of delayed transplantation because of the need for a negative prospective cross-match with a specific cardiac donor without which the risk of acute rejection is raised.

After primary graft dysfunction, the most common cause of mortality in the first month following transplantation is bacterial infection. The debilitated patient with cachexia due to end-stage heart failure who undergoes a major operation followed by aggressive immunosuppression is a setup for a perioperative infection. Thorough attention to measures that reduce this excessive risk is mandatory. Early extubation and removal of invasive lines and drains, aggressive pulmonary toilet, early physical therapy, and appropriate use of perioperative antibiotics are well-understood measures to reduce risk. In addition, preoperative nutritional support with specially designed dietary supplements has been shown to reduce the risk of wound infection in patients with cardiac cachexia [13]. Intensive insulin infusions to maintain a glucose level between 80 and 110 mg/dl has been shown to reduce septic mortality in a recent randomized trial of cardiothoracic ICU patients [12]. Other randomized trials support the use of high-perioperative FIO2 [42] and wound closure with skin staples (versus subcutaneous suture) [43] to reduce wound infection rates. The recent addition of rapamycin to the immunosuppressive regimen seems to be a great advance for reducing early cardiac allograft vasculopathy and renal toxicity. However, likely

due to its antifibrotic effects, the incidence of wound complications such as dehiscence and seromas seems to be increasing on this agent. Its overall effect on patient morbidity has not been defined.

It appears that acute and chronic rejection is primarily mediated by the indirect pathway of CD4 T-cell activation. This process is due to shedding of donor allo HLA peptides that are taken up and processed by recipient macrophages and B-cells (APC cells or antigen processing cells) that present the donor antigen to a TCR complex on a host T-cell. Acute rejection appears to be associated with anti-MHC class II (DR) antibodies and allopeptides. Recurrent and later rejection appears with intermolecular spreading and T-cell recognition of multiple donor HLA-DR alloantigens [44]. Acute rejection involving either cellular or humoral immunity is at risk for occurring within a week to a few months after transplantation. Although late acute episodes can occur, they often do so in the setting of a change in the balance of immunosuppression versus host immunity. A decrease in the blood level of immunosuppressant either by prescription or drug interaction or an up-regulation in alloreactivity owing to viral infection can cause a late allorejection. Myocardial cytolysis on a protocol endomyocardial biopsy (grade ≥ 3) of an asymptomatic patient is the most common scenario that supports initiating a course of treatment. Noninvasive modalities, including radionuclide scanning for evidence of apoptosis [45], magnetic-resonance imaging [46], echocardiography [47], and intramyocardial EKG recordings [48] have shown good correlation with established high-grade rejections in some studies. However, none of these techniques have demonstrated sufficient predictive value to be included in routine clinical management. The treatment of acute rejection employs intravenous steroids as a first-line therapy for a grade ≥ 3 biopsy. Symptomatic patients (e.g., hemodynamic changes, arrhythmias, fever) are often treated despite lesser grade biopsy results. Thymoglobulin has proven highly effective for steroid-resistant episodes, with less toxicity and risk of malignancy seen with OKT3 [49].

Immunosuppression

Transplantation became established as the gold standard therapy for end-stage heart failure only following the development of a drug regimen that successfully inhibited the primary immune response. In addition to azathioprine (AZA) and cyclosporin (CsA), the regimen following heart transplantation has been based on steroids. Transplant physicians have recognized the benefits of corticosteroids from the very early days of clinical transplantation. These molecules have protean effects that are mediated through intracellular receptors that alter gene transcription [50]. Recent advances in the development of tolerance protocols have suggested that steroids block certain immune signaling pathways necessary to induce donor-specific anergy or suppressor cells [51]. There are suggestions of a decreased incidence of AV with steroid weaning protocols due possibly to the enhancement of tolerance in addition to a reduction in diabetes and dyslipidemia associated with steroids [52].

CsA inhibits the gene activation necessary for IL-2 production. It has recently been administered as a novel microemulsion, Neoral, which has significantly improved its bioavailability and reduced pharmacokinetic variability between patients. Approximately 30% of heart transplant recipients develop nephrotoxicity, the primary toxicity of CSA, which appears to be mediated by the inhibition of prostaglandin metabolites. In 2 recent series, calcineurin inhibition was the sole cause leading to metachronous kidney following heart transplantation [53,54].

Approximately 20% of heart transplant programs use the calcineurin inhibitor FK506 (tacrolimus), which has proven to be at least as effective as CSA in heart transplant recipients [55]. It has found particular success following a switch from CsA-based immunosuppression when faced with a refractory acute heart rejection. Given a similar mechanism of action to CsA, the reason for the improved effectiveness of tacrolimus in refractory rejection likely relates to more predictable pharmacokinetics. Compared to recipients receiving CsA, tacrolimus was found to be associated with less facial disfigurement, hirsutism, hypertension, and hyperlipidemia but equal nephrotoxicity and greater neurotoxic and diabetogenic effects.

The classic antimetabolite has been azathioprine (AZA), which inhibits purine synthesis and therefore DNA and RNA synthesis throughout all dividing cells. Mycophenolate mofetil (MMF) appears to be more selective for T and B cells than AZA [56] based on its ability to block the synthesis of purines in the de novo pathway; lymphocytes, unlike other cells, depend solely on the de novo pathway for purine synthesis. Acute rejection and antibody production are reduced with MMF com-

pared to AZA after heart transplantation [57]. In addition, neutropenia has not been a limiting factor as it has been with AZA.

Rapamycin (sirolimus, RPM) prevents the signaling between IL-2 receptor activation and cell cycle initiation and leads to a cell cycle arrest in B-cells and smooth muscle cells [58]. This antiproliferative effect leads to the arrest of AV in both small [59] and large [60] animal experimental models and the prevention of intracoronary restenosis after using RPM-coated stents [61]. In preliminary randomized studies, the use of RPM instead of AZA following heart transplantation has resulted in reduced AV by IVUS evaluation at 6 months [62] and 1 year [63]. Sirolimus is not nephroxic, but it may enhance the renal toxic effects of calcineurin inhibitors [64]; its main toxicity is hyperlipidemia and wound complications such as dehiscence and seromas.

Combinations of these drugs that act at the level of cytokine production, the proliferative response to cytokines, and/or the signaling between the two have demonstrated additive immunosuppressive effects [65]. This will not only effectively reduce the alloresponse but also potentially do so with lower doses of each.

Polyclonal anti-T cell preparations (ATG) and the murine anti-human CD3 monoclonal antibody (OKT3) recognize T-cell surface structures and kill by inducing F_c-receptor-mediated or complement-dependent cell lysis. Prior experience with ATG and OKT3 as induction agents in thoracic transplantation has demonstrated only a delay in the onset of acute rejection at the expense of a profound, uncontrolled immunosuppression that increases the risk for opportunistic infections and malignancy [66]. As a result, their current use is limited in most centers for the treatment of refractory acute rejection and as a calcineurin inhibitor sparing agent in those with perioperative renal dysfunction. However, the suggestion of clinical tolerance to abdominal transplants following ATG induction therapy deserves close attention in future protocols [67].

The "immunological synapse" between T cells and antigen-presenting cells includes the costimulatory molecules CD28, whose ligand is B7; CD154, which binds to CD40; CD2, the ligand for CD58 (LFA-3); and LFA-1, the ligand for ICAM-1. T cells that have been activated express CTLA-4, which may act as a competitive inhibitor of CD28, thereby blocking the generation of costimulatory signals [68]. Inhibition of costimulation using monoclonal antibodies against ICAM [69], CD40L [51], and CD28 [70] has generated donor-specific tolerance in preclinical transplantation models. Stimulation of alloresponsive T cells in the absence of costimulation seems to be a central feature in this form of tolerance as the addition of immunosuppressive medications such as FK506 or corticosteroids inhibit its development.

The development of a humanized monoclonal antibody (mAb) against the IL-2 receptor provided the clinical opportunity for a more selective targeting of activated T-cells. In a small (55 heart transplant recipients), randomized clinical trial, induction therapy using this mAb, dacluzimab, reduced the frequency and severity of acute rejection events over the study period with essentially no side effects and no increased risk of infections or malignancy [71]. Pilot studies using mAb against the cell adhesion molecules LFA-1 [72] or ICAM-1 [73] showed promise in preventing reperfusion injury but variable success against acute rejection. The combination of the two, which was synergistic against acute rejection in rodent models, has not been tried clinically. Also awaiting clinical trial is a strategy that inhibits T-cell costimulation such as the anti-CD154 mAb or CTLA-4 Ig, which has produced tolerance in the nonhuman primate model [51]. Given our understanding of this redundancy of costimulation, a combination of various mAb would likely be the best protocol to promote T-cell anergy. Unfortunately, no preclinical or clinical trials using a combination strategy have been performed in large part due to financial conflicts between the different pharmaceutical companies that own the rights to these agents.

Chronic Rejection

Although chronic, persistent cell-mediated rejection causes progressive myocardial fibrosis and dysfunction, the term *chronic allograft vasculopathy* (AV) takes into consideration the role of multiple nonimmune factors in the etiology of this process. AV has a prevalence of at least 60% within 5 years of transplantation [74]. This obstructive process can progress to near-complete occlusion of the epicardial coronary arteries causing microinfarction and macroinfarction and is the leading cause of death after the first year following cardiac transplantation**.** The histologic findings differ from those seen in typical atherosclerosis, with a uniform pattern of near-luminal occlusion by neointimal proliferation, fewer early accumulations of extracellular lipid, and infiltrates of T cells that encircle the entire vessel [75]. The concentric nature of the lesion has led

to emergence of intravascular ultrasound (IVUS) as the optimal method for clinical detection of AV [76]. Endothelial cells generally remain intact but are known to be dysfunctional based on a paradoxical constrictive response to acetylcholine [77]. The determination of coronary flow reserve using an intracoronary doppler wire further complements IVUS in the evaluation of allograft vasculopathy. Because abnormalities in flow reserve most often reflect microvascular disease, this analysis is particularly important to detect early stage disease.

AV has been linked to multiple potential etiologies, but the most important clinical explanation has not emerged. The usual risk factors for atherosclerosis in the candidate prior to transplant such as hyperlipidemia, smoking, or diabetes are not predictors of AV. However, after transplantation, the development of metabolic markers of insulin resistance including hyperglycemia, hyperinsulinemia, and dyslipidemia predicted cardiac death [78]. Treatment of posttransplantation hyperlipidemia was shown in another randomized trial to reduce the incidence of AV [79]. Cytomegalovirus (CMV) infection might prompt the atherosclerotic process, but it has been clearly demonstrated that cytomegalic infection is not required for the process to occur [80]. Antidonor cellular and humoral immune responses are associated with clinical AV lesions, but these processes might equally well be a marker for high risk as opposed to a direct cause of chronic rejection. Events around the procurement process that result in early endothelial activation and dysfunction have demonstrated a convincing correlation with the development of AV [74]. Evidence that genetics plays a role in these events is supported by the finding that a specific TGF β genotype (i.e., proline at codon 10) was found to be associated not only with the development of AV [81] but also with the development of chronic nephrotoxicity from CSA [82]. Despite a significant improvement in the 1-year half-life of allografts in the modern CSA era of improved immunosuppression, AV has remained refractory [83]. Increased expression of ICAM-1 and other adhesion molecules in AV lesions [84] points to the role of a smoldering, nonspecific immune response in the chronic rejection process as documented in development and activation of nontransplant atherosclerosis [85].

Our current limited pathophysiologic understanding of this relentless process is based largely on small animal models. By systematically isolating possible etiologic factors, these models have provided significant insight into the basic science of the vasculopathy process in cardiac allografts. However, out of logistical necessity, the surrogate pathologic lesion occurs much earlier than the typical changes of chronic rejection in clinical patients. Thus, the pathogenesis of the process being studied experimentally is almost certainly not the same as that occurring clinically. Indeed, many of the commonly used rodent models demonstrate suppression of AV lesion formation with standard immunosuppression such as CSA [53], a finding that significantly limits clinical relevance. Clinical application of hypotheses generated from large animal models will be the most likely route of making an impact on this problem.

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